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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

STANDLEY, STEVEN H

ART UNIT PAPER NUMBER

1649

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/723,940

Applicant(s)

LEONARD ET AL.

Examiner

Steven H. Standley

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 April 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5-8 and 26-38 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 7,8 and 37 is/are allowed.
- 6) ☒ Claim(s) 1-2, 5-6, and 26-36, and 38 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of -86 C to T and sequencing as species in the amendment of 4/17/07 is acknowledged.
2. Applicant has cancelled claims 3-4, and 9-25. Claims 1-2, 5-8, and 26-38 are under consideration.

Response to Amendment

3. The amendments filed 12/11/06 and 4/17/07 have been made of record. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Rejections/Objections: withdrawn.

Claim Objections

4. Objection to claim 1 for informal grammar is withdrawn due to applicant's amendment.

Claim Rejections - 35 USC § 112

5. Rejection of claims 1-8, and 22-25 under 35 USC § 112, 1st paragraph, enablement is withdrawn due to applicant's amendment. However, see the rejection under 35 USC § 112, 1st, scope of enablement below.
6. Rejection of claims 1-6, and 22-25 under 35 USC § 112, 2nd paragraph, is withdrawn due to applicant's amendment.
7. Rejection of claims 1-3, and 22 under 35 USC § 112, 2nd paragraph, is withdrawn due to applicant's amendment.

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8. Rejection of claims 7-8 under 35 USC § 112, 2nd paragraph, is withdrawn due to applicant's amendment.

Claim Rejections - 35 USC § 102

9. Rejection of claims 1, 5, 6, and 22-24 under 35 USC § 102(b), is withdrawn due to applicant's amendment.

Rejections/Objections: maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-2, 5-6, and 26-33, 35-36, and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying individuals with increased likelihood of having schizophrenia comprising providing a nucleic acid from a human subject, detecting the presence of a -86 C to T substitution in relation to a start codon of said alpha 7 allele beginning at residue 270 of SEQ ID NO: 125, does not reasonably provide enablement for "detecting the presence of at least one polymorphism within a core promoter region corresponding to SEQ ID NO: 125 of said alpha 7 allele wherein said at least one polymorphism contributes to reduced transcription. Furthermore, the specification does not reasonably provide enablement for the used of any of the other variants as indicators that a human subject is predisposed to schizophrenia. The specification does not enable any person skilled in

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the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to:

1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a method to identify individuals predisposed to schizophrenia by correlating the presence of a polymorphism in the alpha-7 nicotinic receptor allele with a predisposition to schizophrenia. The method further recites diagnosis and differential diagnosis in claims 37 and 38. The method is complex because reciting "polymorphisms within said alpha-7 allele that contribute to reduced transcription" other than the ones disclosed in the specification are not predictable and are completely unknown without undue further experimentation. Further, there is only a significant correlation between mutant -86 C to T and schizophrenia. The rest of the variants have no significant relationship to schizophrenia, as disclosed in the prior art (see Leonard et al., page 1091, left column). Furthermore, of the variants that are characterized as being more abundant in schizophrenics versus controls, the expression level is both increased and decreased (see Leonard et al, page 1091 left

column, and Leonard et al, page 1092 for expression. Thus, the expression is modified independent of the relative abundance of the variant. Therefore there is no reliable relationship between schizophrenia and all the variants save -86 C to T, and there is no reliable relationship between expression and schizophrenia. It is also not predictable whether or not a generic variant of the alpha-7 allele will mark a predisposition to schizophrenia. Also, with respect to diagnosis and differential diagnosis of schizophrenia the invention is complex because diagnosis would involve multiple genes and environmental factors that are currently not taught.

The state of the art at the time of filing is that there is no way to genetically diagnose schizophrenia and that linkage analysis has suggested that there are multiple genes with small effects and incomplete penetrance (see abstract and page 28, right col top, Miyamoto et al., 2003). Further, the art does not teach all variants of the alpha-7 nicotinic receptor allele and does not teach that every allelic variant or polymorphism is related to schizophrenia. The post-filing date art also teaches no relationship between the expression levels of the alpha-nicotinic receptor and schizophrenia, and further indicates it is correlated with bipolar illness (see Deluca et al, Abstract.). Thus, the art teaches that a decreased expression of alpha-7 nicotinic receptor is not diagnostic of schizophrenia, as it relates to claims 7 and 37.

The level of predictability of the art is low. In particular, the specification identifies some promoter variants that decrease expression of the alpha-7 receptor, but any newly discovered polymorphism would not necessarily result in effects on the receptor expression or function. Therefore the predictability of the relationship between

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schizophrenia and polymorphisms of the alpha-7 gene is very low. Also, since there is currently NO method of genetic diagnosis of schizophrenia the predictability of a genetic diagnostic for schizophrenia is nil. Applicant demonstrates one example of a variant that is significantly elevated in schizophrenia that also decreases expression. The other example variants variably increase or decrease expression and have no significant elevation in schizophrenia. Therefore variants that are elevated in schizophrenia do not decrease expression and variants that decrease expression are not significantly associated with schizophrenia.

There are no working examples that diagnose schizophrenia by obtaining and genotyping an alpha-7 allele in a patient. There are also no examples that teach that every variation in the alpha-7 allele is predictive of predisposition or is diagnostic for schizophrenia. There are no examples of differential diagnosis. There is no guidance in the specification as to how to make a genetic diagnosis of schizophrenia with the current method. There is also no guidance as to how to recognize a polymorphism in the alpha-7 allele that is significantly correlated with schizophrenia.

Applicant points out that several of the claims do not require diagnosis. This is not found persuasive because, with the exception of the -86 C to T substitution, none of the variants establish a predisposition to schizophrenia because there is no significant relationship between their frequency and schizophrenia.

Therefore, because of the complex nature of the invention, the lack of predictability of the art, the contrasting teachings in the art, and the lack of guidance or

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example in the specification, it would require one of skill in the art undue experimentation to make or use the invention as currently claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, and 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites "b) detecting the presence of at least one polymorphism within a core promoter region corresponding to SEQ ID NO: 125 of said alpha-7 allele." I'm not sure how to construe this limitation. Does it mean that "said alpha-7 allele" comprises SEQ ID NO: 125? Or does it mean detecting the presence of at least one polymorphism within a core promoter region of said alpha-7 allele corresponding to SEQ ID NO: 125?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Rejection of claim 2-6, 26-36 under 35 USC § 102(a) is maintained for the reasons made of record in the office action dated 6/06/06. Applicant's arguments have been fully considered and not found to be persuasive. Applicant argues that Leonard et al is not prior art and further indicates that the amendment of 12/11/06 is accompanied by a "Leonard declaration." The Examiner notes that no such declaration is evident in the file. Moreover, there are many authors on the publication of Leonard et al and only two (Leonard and Freedman) are listed as inventors herein. A signed statement indicating the other authors were merely working under the named inventor's supervision is required to overcome this prior art rejection. See *In re Katz*, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). Also, see MPEP 2132.01. It is suggested that applicant resubmit a Katz declaration to obviate the rejection.

Conclusion

Claims 7-8, and 37 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not

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mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven Standley whose telephone number is **(571) 272-3432**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on **(571) 272-0849**.


The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Steve Standley, Ph.D.

7/23/07




DAVID S. ROMEO
PRIMARY EXAMINER